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(54) Subcutaneous silicone implant

(57) A subcutaneous implant is provided for promoting growth in livestock and comprises a substantially hollow cylindrical component of silicone rubber, especially a dimethylpolysiloxane rubber, impregnated with a growth promoting amount of oestradiol. The implant has a core consisting of an active ingredient dispersed in a biocompatible, biosoluble polymeric material e.g. polyethylene glycol which dissolves within days of implantation. The active ingredient may be a drug, a hormone or a vaccine.

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SPECIFICATION

Subcutane us Implant

This invention relates to subcutaneous implants and, in particular, to an oestradiol subcutaneous implant for use in promoting growth in livestock.

Subcutaneous oestradiol implants for the promotion of growth in ruminants are known. U.K. Patent Publication GB 2 030 044 A describes a solid, cylindrical subcutaneous implant for ruminants which has a biocompatible inert core and a biocompatible coating of oestradiol embedded in a dimethylpolysiloxane rubber. Release of oestradiol from the implant is determined by the surface area of the implant. With such an implant one observes a transitory increase in sexual activity in some of the implanted animals. However, this heightened sexual activity is generally only observed in about 2% of the animals.

It is also known that one can achieve a constant release of a steroid from silicone rubbers such as dimethylpolysiloxane (DPS) since the rubbers are readily permeable to steroids. Silicone rubbers such as DPS are found to be useful in implants because they do not cause foreign body reactions even after prolonged periods. After the implant has been exhausted, an empty hull of foreign material is left embedded in the tissue and can be removed and replaced by a fresh implant.

The administration of oestradiol to animals is considered to have two major effects. Firstly, it stimulates the release of growth hormone and secondly, recent work has indicated the presence of specific oestradiol receptors in muscle which results in oestradiol acting locally on muscle to stimulate growth. Furthermore, the administration of oestradiol bulls suppresses testicular development resulting in a reduced aggressiveness and easier farm management. Oestradiol administration effectively achieves a hormonal "castration" of male animals.

It is an object of the present invention to provide an improved subcutaneous implant for the sustained release of oestradiol and which includes means for ensuring a rapid release of a further active ingredient to an animal.

Accordingly, the invention provides a subcutaneous implant for promoting growth in livestock, which comprises a substantially hollow cylindrical component of silicone rubber impregnated with a growth promoting amount of oestradiol, said component having a core consisting of an active ingredient dispersed in a biocompatible, biosoluble polymeric material which dissolves within days of implantation.

Preferably the livestock is represented by poultry or a ruminant animal.

Preferably, the oestradiol is present in the silicone rubber component at a concentration of from 10—30% by weight, especially 20% by weight.

The silicone rubber is preferably a dimethylpolysiloxane (DPS) rubber. Especially preferred dimethylpolysiloxanes are those known generically as Silastic such as Silcoset sold by ICI plc or Silastic 382 and MDX-4-4210 sold by the Dow Corning Corporation. Such silicone rubbers consist of two components—a first component consisting of liquid, uncured rubber and a second component including a curing agent. The first and second components are mixed and allowed to cure.

The biocompatible, biosoluble polymeric material defining the core of the implant is any biocompatible polymeric material which readily solubilizes *in vivo* at body temperature and/or when it comes into contact with a body fluid.

A preferred polymeric material is polyethylene glycol. A preferred polyethylene glycol is one having a molecular weight in the range 3,000—10,000, especially 4,000—5,000, in admixture with an equal portion of a polyethylene glycol having a molecular weight in the range 200—600, especially 300—400.

The active ingredient may be a drug, hormone or vaccine.

Suitable drugs include anthelmintics such as Levamisole or Ivermectin sold under the Trade Mark Ivomec or other suitable water-soluble anthelmintic.

Suitable steroids include an anabolic steroid, progesterone or testosterone.

When the active ingredient is progesterone, one obtains an implant which is suitable for counteracting the transitory heightened sexual activity observed in certain animals when oestradiol only is administered by way of an implant.

Suitable vaccines include a black leg vaccine, an anti-clostridial vaccine sold under the Trade Mark Tribovax T or a salmonella vaccine sold under the Trade Mark Mellavax.

The core may also include a mixture of said active ingredients. The choice of active ingredient(s) is determined by the particular effect(s) which it is desired to elicit in an animal.

The dissolution time of the core is preferably 3—4 days.

The implant is preferably 5—100 mm. in length, more especially 20—40 mm. The hollow cylindrical component preferably has a wall thickness of 0.1 to 2 mm, especially 1.0 mm. The diameter of the core is preferably 1 to 10 mm, especially 3 mm.

The invention also provides a method of promoting growth in livestock, which comprises implanting in an animal an implant as hereinabove described.

When the animal is a ruminant animal the implant is preferably implanted in the ear. It will be appreciated that the implant is desirably implanted in a portion of the body which is not destined for human consumption.

One method of manufacturing a subcutaneous implant as hereinabove described comprises the steps of:

(a) centering a first tube in a second tub s as to leave a space therebetween corresponding to th desired wall thickness of the cylindrical c mponent;

(b) filling the space with a liquid silicone rubber containing oestradiol and allowing the silicone rubber to cure; and

(c) removing the inner tube and filling the resulting core with a filling quantity of active ingredient dispersed in a biocompatible, biosoluble polymeric material and causing the polymeric material to solidify.

The invention will be further illustrated by the following Examples

EXAMPLE 1

Oestradiol (1 g.) (supplied by Sigma Limited, UK) was thoroughly mixed with (4 g.) component 1 of Medical Grade Silastic 382. Component 2 (0.05 g; 1%) of Silastic 382 (curing agent) was added and the materials were remixed and poured into a space 5 mm in thickness defined between a pair of centered tubes 120 mm in length. The oestradiol/silastic mixture was allowed to harden.

When the mixture had hardened the inner tube was removed. A mixture of progesterone (200 mg) in polyethylene glycol (M.W. 4.000) (159 mg) and polyethylene glycol (M.W. 300) (159 mg) was prepared and heated to 50°C. The mixture was poured into the core defined by the hardened silastic. The mixture was allowed to cool to room temperature and solidified. The outer tube was then removed and the implants were prepared therefrom by cutting into 30 mm lengths. The implants so formed are optionally sterilized in plastic packets.

EXAMPLE 2

Example 1 above was repeated except that the progesterone was replaced by Ivermectin in an amount sufficient to obtain an implant containing Ivermectin in a concentration of 20 mg per kg body weight.

Determination of Release Rate

In vitro release rate was determined by incubating the implants for 24 hours at 37°C with continuous shaking in Erlenmeyer flasks containing 30 mm 0.9% saline (Dziuk, P. J., and Cook, B. 1966 Endocrinology *78*, 208). The amount of oestradiol released into the medium was measured in a SP 800 Unicam Spectrophotometer at 280 nm following the extraction of oestradiol with methanol.

The *in vivo* release rate in the ear of heifers was estimated by measuring the fall in oestradiol concentration of the implant after it had been in the ear for known periods of time. After removal of the implant from the animals, the oestradiol was extracted by refluxing with methylene chloride for 24 hours. After evaporation of the methylene chloride with oxygen-free nitrogen, the oestradiol was then taken up in 2 l of methanol. The concentration of oestradiol in the solution was determined in the spectrophotometer at 280 nm. No corrections were made for procedural losses but extraction of implants of known concentration indicated that recovery rates were over 90%.

Field Trials

Field trials were carried out as follows: a group of animals (heifers or steers) were selected and randomised into two groups. One group of animals served as controls and the other group were implanted with subcutaneous implants prepared as in Example 1. The animals were weighed prior to implantation and at regular intervals (2—4 weeks) thereafter. The control animals were similarly weighed.

The results of these field trials are shown in Table 1.

TABLE 1

A. Steers—Trial 1

	N (number of animals)	Initial Weight (kilos)	Weight on Day 196 (kilos)	Gain after 196 days
Control	5	285.0	459.2	174.2
Implant of Example 1	4	266.5	475.2	208.7

B. Steers—Trial 2

	N (number of animals)	Initial W ight (kilos)	Weight on Day 146 (kilos)	Gain after 146 days
Control	9	155.7	275.9	120.2
Implant of Example 1	9	153.9	285.3	131.4

TABLE 1 (contd.)
C. Heifers—Trial 3

	N (number of animals)	Initial Weight (kilos)	Weight on Day 98 (kilos)	Gain after 98 days
Control	5	223.0	283.2	60.2
Implant of Example 1	5	208.8	291.6	82.8

The results show in each case (Trials 1, 2 and 3) a significant increase in weight in the animals implanted with the subcutaneous implant of Example 1 over the period of the trial.

A trial (4) was also carried out to determine the daily liveweight gain of steers less than one year old, 150 days after implantation with oestradiol implants prepared according to Example 1. The results of this trial are given in Table 2.

TABLE 2

Treatment	No. of Steers	Initial Wt. (kg)	Daily live Wt. gain (kg/day)
Control	11	238	0.78
Implant of Example 1 (5 mm×30 mm)	10	214	1.00

Another trial (5) was carried out to determine the daily liveweight gain of steers more than one year old, 150 days after implantation with oestradiol implants prepared according to Example 1. The results of this trial are given in Table 3.

TABLE 3

Treatment	No. of Steers	Initial Wt. (kg)	Daily live Wt. gain (kg/day)
Control	16	387	0.76
Implant of Example 1 (5 mm×30 mm)	18	367	1.10

The steers subjected to trials (4) and (5) showed no abnormal behaviour. As indicated in Tables 2 and 3 significant increases in growth rate were observed.

CLAIMS

1. A subcutaneous implant for promoting growth in livestock, which comprises a substantially hollow cylindrical component of silicone rubber impregnated with a growth promoting amount of oestradiol, said component having a core consisting of an active ingredient dispersed in a biocompatible, biosoluble polymeric material which dissolves within days of implantation.

2. A subcutaneous implant according to Claim 1, wherein the oestradiol is present in the silicone rubber component at a concentration of from 10—30% by weight.

3. A subcutaneous implant according to Claim 1 or 2, wherein the oestradiol is present in the silicone rubber component at a concentration of 20% by weight.

4. A subcutaneous implant according to any one of Claims 1 to 3, wherein the silicone rubber is a dimethylpolysiloxane rubber.

5. A subcutaneous implant according to any one of Claims 1 to 4, wherein the biocompatible, biosoluble polymeric material defining the core of the implant is any biocompatible polymeric material which readily solubilizes *in vivo* at body temperature and/or when it comes in contact with a body fluid.

6. A subcutaneous implant according to Claim 5, wherein the polymeric material is polyethylene glycol.

7. A subcutaneous implant according to Claim 6, wherein the polyethylene glycol polymeric material consists of a polyethylene glycol having a molecular weight in the range 3,000—10,000 in admixture with an equal portion of a polyethylen glycol having a molecular weight in the range 200—600.

8. A subcutaneous implant according to Claim 7, wherein the polyethylene glycol polymeric material consists of a polyethylene glycol having a molecular weight in the range 4,000—5,000, in admixture with an equal portion of a polyethylene glycol having a molecular weight in the range 300—400.

9. A subcutaneous implant according to any one of Claims 1 to 8, wh rein th active ingredient is a drug, a hormone, a vaccine or a mixture thereof.

10. A subcutaneous implant acc rding to Claim 9, wherein the drug is an anthelmintic.

11. A subcutaneous implant according to Claim 10, wherein the anthelmintic is Levamisole or Ivermectin.

12. A subcutaneous implant according to Claim 9, wherein the active ingredient is a steriod.

13. A subcutaneous implant according to Claim 12, wherein the steroid is an anabolic steroid.

14. A subcutaneous implant according to Claim 12, wherein the active ingredient is progesterone.

15. A subcutaneous implant according to Claim 12, wherein the active ingredient is testosterone.

16. A subcutaneous implant according to Claim 9, wherein the active ingredient is a vaccine selected from a black leg vaccine, an anti-clostridial vaccine or a salmonella vaccine.

17. A subcutaneous implant according to any preceding claim, which is 5—100 mm in length.

18. A subcutaneous implant according to Claim 17, which is 20—40 mm in length.

19. A subcutaneous implant according to Claim 18, which is 30 mm in length.

20. A subcutaneous implant according to any preceding claim, wherein the hollow cylindrical component has a wall thickness of 0.1—2 mm.

21. A subcutaneous implant according to Claim 20, wherein the hollow cylindrical component has a wall thickness of 1 mm.

22. A subcutaneous implant according to any preceding claim, wherein the diameter of the core is between 1 and 10 mm.

23. A subcutaneous implant according to Claim 22, wherein the diameter of the core is 3 mm.

24. A method of manufacturing a subcutaneous implant according to any preceding claim, which comprises the steps of:

(a) centering a first tube in a second tube so as to leave a space therebetween corresponding to the desired wall thickness of the cylindrical component;

(b) filling the space with a liquid silicone rubber containing oestradiol and allowing the silicone rubber to cure; and

(c) removing the inner tube and filling the resulting core with a filling quantity of active ingredient dispersed in a biocompatible, biosoluble polymeric material and causing the polymeric material to solidify.

25. A method of promoting growth in livestock, which comprises implanting in an animal an implant as claimed in any one of Claims 1—23.

26. A method according to Claim 25, wherein the livestock is poultry.

27. A method according to Claim 25, wherein the livestock is a ruminant animal.

28. A subcutaneous implant according to Claim 1, substantially as hereinbefore described with particular reference to Examples 1 and 2 of the accompanying Examples.

29. A method according to Claim 25 of manufacturing a subcutaneous implant, substantially as hereinbefore described with particular reference to Examples 1 and 2 of the accompanying Examples.

30. A subcutaneous implant whenever manufactured by a method claimed in Claim 24 or 29.

31. A method according to Claim 25 for promoting growth in livestock, substantially as hereinbefore described with particular reference to the accompanying field trials.

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